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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,380	07/03/2003	Wendell Lim	UCSF03-114	5261

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RICHARD ARON OSMAN
4070 CALLE ISABELLA
SAN CLEMEMTE, CA 92672

EXAMINER	
SKIBINSKY, ANNA	
ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/613,380	LIM ET AL.	
	Examiner	Art Unit	
	Anna Skibinsky	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/11/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,8 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,8 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief filed on 3/11/2007, PROSECUTION IS HEREBY REOPENED. A new grounds of rejection set forth below. To avoid abandonment of the application, appellant must exercise one of the following two options: (1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or, (2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid. A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

Listing of References

The listing of references in the specification (pages 27-28) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112-1st paragraph

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an autoregulated fusion protein with an N-WASP output domain, PDZ and SH3 input domains (with the domains in this order in the sequence), wherein the input domains cooperatively regulate the output domain as an AND-gate, does not reasonably provide enablement for an autoregulated protein with all of the output and input domains listed in the Tables of the specification or for the . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification does not provide guidance for making an autoregulated protein with a set of interacting input and output domains other than with an N-WASP output domain and PDZ and SH3 input domains, wherein said domains are in the order of N-WAST output domain is linked to the PDZ input domain (specification, page 22, lines 4-6) and the PDZ and SH3 input domains are linked to one another (specification, page 25, lines 17-23). There is insufficient guidance for engineering any autoregulated fusion protein that will "allosterically and external, ligand dependently regulate the output domain.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6)

the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims.

(1) the quantity of experimentation necessary to successfully create a polynucleotide chimera that will express a protein is large. The specification lists a multitude of domains and recites in claim 1 that the protein's input domains will regulate the output domains. The description describes in the "Detailed Example" (pages 20-27) for the making of function of an autoregulated protein with an N-WASP output domain, SH3 and PDZ input domains. The description does not provide detailed guidance on how to achieve the synthesis of such an autoregulated protein using all of the domains listed in the specification.

(2) The description describes generating an autoregulated fusion protein with an N-WASP output domain, SH3 and PDZ input domains. The description does not provide detailed guidance to make and use autoregulated fusion proteins with the other input and output domains listed in the specification.

(3) The description provides a working example describing an autoregulated protein with an N-WASP output domain, SH3 and PDZ input domains. The description does not provide a representative sample of experiments to cover the multitude of input and output domains that are recited as being able to comprise such an autoregulated protein. The one Detailed Example is insufficient to describe the making of an autoregulated protein for any of the domains listed in the specification and only describes the one specific autoregulated protein with an N-WASP output domain, SH3 and PDZ input domains.

(4) The nature of the invention is complex and there is insufficient description in the specification to enable the making and use of the multitude of different autoregulated proteins

possible with various combinations of output an input domains listed in the Tables. There is not enough in the specification to enable a general autoregulated protein that will "allosterically and external, ligand-dependently regulate the output domain" for all the domains listed in the specification. The only autoregulated protein described in the specification is one with an N-WASP output domain, SH3 and PDZ input domains. The complexity of creating a fusion protein that will function properly as described in claim 1 warrants more examples and descriptions to enable the invention.

(5) the state of the prior art teaches making fusion proteins but it does not teach autoregulated fusion proteins. The state of the art teaches that there is uncertainty if certain combination of domains will result in a functioning or soluble fusion protein. Cunningham et al. teach that Trx as a fusion partner is used to overcome the problem of inclusion body formation, which is an indication of inappropriate protein folding. Cunningham et al. further teach that it is generally advisable "to explore potential fusion constructs as bacterial expression among these options can be unequal." (page 378, col. 1, par 3). This amounts to undue experimentation. Kim teaches recombinant immunotoxins in which the PE domain has been replaced with the Fv portion of an antibody, forming a fusion protein (Abstract, page 86, col. 1, par 1). Kim teaches that many recombinant immunotoxims have been produced as inclusion bodies and though steps can be taken to solubilize and refold the inclusion bodies, the refolding process does not always produce a native protein and several attempts to refold the scFvs under various conditions yielded very low amounts with poor specific activity (page 88, col. 2, par 2). Clark teaches that expression of genetically engineered proteins in bacteria often results in the accumulation of the protein product in inactive insoluble deposits inside the cell (i.e. inclusion bodies) (page 202,

col. 1, par 1). Pedelacq et al. teach attempts at protein engineering where protein domains thought to improve solubility were directed into inclusion bodies, expressed in E. coli but nevertheless failed to improve solubility (page 927, col. 2, par 2). In terms of structure prediction, Baker et al. teach that accuracy of a comparative model is related to the percentage of sequence identity of which it is based, correlating the structure and sequence similarity of two proteins (page 93, col. 3, par 2). Seffernick et al. teach the expression of two proteins, melamine deaminase which is 98% identical to atrazine chlorohydrolase but is functionally different (page 2405, Abstract). Furthermore, Seffernick et al. teach that though the structure of proteins with similar sequence identity may also be similar, the functions of the proteins are not predictable, as in the example of two proteins with 56% sequence identity, similar three dimensional structure but that do not catalyze the other's reaction (page 2409, col. 1, par 3).

(7) It is highly unpredictable if the combination of domains listed in the specification will successfully lead to an autoregulating protein where the input domains interact with each other and regulate the output domain. Though the idea of creating such a protein is expressed in the specification, there is insufficient evidence that the protein is enabled for all the listed domains. Baker et al. teach that in order to determine protein structure, the sequence should have higher than 30% sequence identity to an already known structure (page 95, col. 2, par 1). Since, the instant application is directed to autoregulated fusion proteins that have not been taught in the prior art and are not taught as having being made (except for one example) by the specification, there is no sequence or known structure with which to make a comparison for structure prediction. Thus is not possible, based on an unavailable sequence and similar template sequence for comparison, to predict the actual structure and/or function of the resulting autoregulated

fusion protein from the domains listed in the specification or whether the fusion the domains will result in a successfully functioning autoregulated protein.

(8) The breath of the claims are extremely broad

The skilled practitioner would first turn to the instant description for guidance in using the claimed invention. However, the description lacks clear evidence that any of the combination of domains listed in the specification, other than the N-WASP, PDZ, and SH3, will successfully lead to an autoregulating protein where the input domains interact with each other and regulate the output domain. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not discuss autoregulated fusion proteins comprising output domains and input domains where the input domains interact with each other to allostericaly and external ligand-dependently regulate the output domain. Finally, said practioner would turn to trial and error experimentation to determine a proper relationships for input and output domains that will perform protein self-regulation as claimed. Such amounts to undue experimentation.

Reply to Arguments

2. Applicant's arguments filed June 17, 2006 have been fully considered but they are not persuasive.

3. Applicants argue that "[t]he test for enablement is whether the specification enables one of skill in the art to practice the invention as claimed without undue experimentation" (Remarks, page 5, lines 13-13).

4. In response, the argument presented is not directed to the merits that form the basis of the instant scope of enablement rejection. While some embodiments of the claim are acknowledged

as enabled, one of skill in the art must resort to undue experimentation in order to discern the enabled embodiments of the claim from the non-enabled embodiments, for example for various output domains recited in the disclosure (specification, page 6, line 20 to page 7, line 14).

5. Applicants argue the potential of generating auto regulated fusion protein from input and interacting domains from data bases as well as mutating domains to provide binding partners (Remarks, page 6 line 17 to page 7, line 9) yet, undue experimentation is nonetheless required to determine whether what applicants claim will work for the numerous domains listed by applicants.

6. Applicants argue that "[a] wide variety of external ligands may be used to activate the switches by interacting with one or more of the input domains," (page 7, lines 21-29) however, applicants provide no evidence in the disclosure that they were in the posession of the "wide variety" autoregulating fusion proteins derived from the variety of domains and external ligand regulators.

7. Applicants argue that the specification "enables one skilled in the art to make and use without undue experimentation an autoregulated fusion protein comprising an output domain and a plurality of input domains," but only provide evidence of success with one combination of domains (i.e. N-WASP output domain, SH3 and PDZ input domains). The enablement of a general autoregulating fusion protein, as recited in claim 1, requires a broader sample of examples and descriptions in the disclosure.

Objection to Claims

Claim 14 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Skibinsky whose telephone number is (571) 272-4373. The examiner can normally be reached on 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER